REMARKS:

By this Amendment, applicant has canceled all previous pending claims without prejudice and has introduced new claims 170-238 to be the basis for further examination. Support for new claims 170-238 may be found inter alia, in the previously pending claims, and in the specification. The new claims are fully supported by the application and claims as filed, and no new matter has been introduced into the application by virtue of the amended and new claims. Specifically, claims 170-238 find support in the instant specification, *inter alia*, on page 3, lines 16-16, on page 7, lines 21-23, on page 9, lines 20-23 and on page 18, lines 25-27; and on page 32, lines 15-16; and on page 22, line 1, and on page 24, lines 19-20; and on page 17, lines 8-11. Thus, applicant maintains the new claims 170-238 are fully supported by the specification and raise no issue of new matter. Applicant requests that the Examiner enter these new claims.

In addition, the specification of the instant application has been amended to correct grammatical and typographical oversights that have come to the attention of the applicant, and to address the Examiner's objection pertaining to the term GSSM as set forth in the November 27, 2002 Office Action.

The Examiner remarks that this application contains claims 31, 33-40, 52, 54, 56, 59-62, 88, 90-97, 112-115 and 118, which "are drawn to an invention nonelected with traverse in Paper No. 8". However, in the restriction requirement (Paper No. 5), the foregoing claims 31 and 33-40 were not formally placed into any of the seven groups identified by the Examiner as allegedly being drawn to distinct inventions. It is believed that, upon allowance of one or more generic claim(s), applicants are entitled to consideration of claims to additional species, which are written in dependent form or otherwise include all the limitations of an allowed generic claim.

(37 C.F.R. §1.141). Should one or more generic claims be found allowable, applicant preserves the right for consideration of one or all of the listed claims which were not formally restricted into the groups as recited by the Examiner in Paper No. 5.

Information Disclosure Statement

Pursuant to 37 C.F.R. §§1.56 and 1.97(b), Applicants bring to the attention of the Examiner the following documents listed on the attached PTO Form 1449 (**Exhibit A**). This Information Disclosure Statement is being filed as part of a submission with a Request for Continued Examination and is therefore submitted as both timely and proper.

Copies of references are available in parent file U.S. Serial No. 09/535,754, filed March 27, 2000, now U.S. Patent No. 6,361,974, issued March 26, 2002 and parent file U.S. Serial No. 08/651,568, now U.S. Patent No. 5,939,250, issued August 17, 1999.

Applicants state that some of the documents listed on the attached PTO Form 1449 were cited in an International Search Report issued in connection with PCT International Application No. PCT/US01/29712. A copy of the International Search Report and copies of the documents cited therein are attached hereto (**Exhibit B**). It is respectfully requested that the Examiner initial and return a copy of the enclosed PTO Form 1449 with the next Patent Office communication.

Objections

The Examiner has objected to the instant disclosure and states that the passage on page 90, "a mini-ultracentrifuged at 45k rpm at 20°C for four hours", is not adequate description of a

centrifugation experiment, as the rotor or the gravitational force must be identified in order to allow one skilled in the art to reproduce the experiment.

In reply, applicant maintains his position set out in the previous amendment filed in connection with this application and believes the discussions with the Examiner during the recent Examiner Interviews with regard to this objection and the previous comments have obviated this ground of rejection. Applicant requests the Examiner reconsider and withdraw this ground of rejection.

The Examiner states that the primers in the PCR experiment on page 96, line 14, are not described or identified by sequence identification numbers. The Examiner responds to applicant's arguments by saying that the experiment on page 96 is directed to the mutagenesis of a specific enzyme (9N2 beta-glycosidase). According to the Examiner, "[i]n order for an ordinary skill in the art to repeat the disclosed experiment ... would want to know either the sequence of said glycosidase or the primer in addition to the source of DNA".

It is respectfully submitted that no such identification is required because the description on page 96 does not represent a sequence, *i.e.,* an unbranched sequence of 10 or more nucleotides, that requires representation by a sequence identification number under 37 C.F.R. §§1.185 *et seq.*. Only if an unbranched sequence of 10 or more nucleotides is present in the application is a sequence identification number required. Because this particular location of the application contains no such sequence, there is no requirement to identify the reference to the primer by a sequence identification number.

The Examiner has objected to claims 16 and 76 (reciting enzymes) and claims 21, 82, 156 and 165 (reciting extremophiles) under 37 C.F.R. §1.75(d)(1) as being in improper form for stating improper Markush groups.

In reply, without conceding the correctness of the objection, the above claims have been cancelled and new claims have been added that obviate the Examiner's concerns regarding improper form of the claims under 37 C.F.R. §1.75(d)(1).

Provisional Double Patenting Rejection under 35 U.S.C. §101

Claims 63, 109, 110, 116, 119, 120, 132, 136-138 and 141-142 have been provisionally rejected under 35 U.S.C. §101 as claiming the same invention as that of Claims 41-49, 52, 55, 56, 60, 62, 63, 68 and 69 of copending application U.S. Serial No. 09/375,605. It is believed that the Section 101 provisional double patenting rejection has been overcome in view of the cancellation of the relevant claims in the instant application.

Rejections Under Doctrine of Obviousness-Type Double Patenting

Claims 1-30, 32, 41-51, 53, 55, 57, 58, 63-87, 89, 98-111, 116, 117 and 119-169 have been rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 5,939,250, in view of the prior art as exemplified by Stemmer et al. (U.S. Patent No. 5,605,793).

Claims 1-30, 32, 41-51, 53, 55, 57, 58, 63-87, 89, 98-111, 116, 117 and 119-169 have been rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 5,958,672 in view of the prior art as

exemplified by Arnold et al. (U.S. Patent No. 5,316,935) and Stemmer et al. (U.S. Patent No. 5,605,793).

Claims 1-30, 32, 41-51, 53, 55, 57, 58, 62-87, 89, 98-111, 117 126, 128, 130, 133-135, 140 and 143-169 have been provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 41-70 of U.S. Patent Application No. 09/375,605 in view of the prior art as exemplified by Arnold et al. (U.S. Patent No. 5,316,935) and Stemmer et al. (U.S. Patent No. 5,605,793)

With respect to the non-statutory double patenting rejections over U.S. Patent Nos. 5,939,250 and 5,958,672 in view of the exemplified state of the art, and without acquiescing to the propriety of each of the rejections, applicant stands ready to submit executed Terminal Disclaimer documents in compliance with 37 C.F.R. §1.321(c), signed by the assignee, and the fee as required by 37 C.F.R. §1.20(d). However, in view of the other issues now remaining in this application, applicant requests that the Examiner hold these rejections in abeyance until the claims are in condition for allowance. At that time, applicant will be prepared to submit the Terminal Disclaimers to obviate these rejections.

With respect to the non-statutory double patenting rejection over co-pending patent application U.S. Serial No. 09/375,605, it is respectfully requested that this rejection be held in abeyance until all other rejections have been officially obviated, and/or the claims have been deemed allowable, in the instant application, and/or in the '605 application. The rejection can be reiterated, as appropriate, in the remaining pending application. Should both the instant application and the pending application be deemed allowable, a Terminal Disclaimer and corresponding fee will be filed in the appropriate case.

Rejections Under 35 U.S.C. §112, second paragraph

Claims 1-30, 32, 41-51, 53, 55, 57, 58, 63-87, 89, 98-111, 116, 117 and 119-169 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite for the reasons as set forth on pages 6-8 of the office action.

Applicant respectfully traverses the rejection and believes that the claims as presented herein address the Examiner's concerns and suggestions, and thus overcome the rejection. Accordingly, withdrawal of the Section 112, second paragraph, rejection is respectfully requested.

Rejections Under 35 U.S.C. §102

Claims 1-6, 8-24, 27, 28, 30, 41-48, 50, 51, 53, 55, 57, 58, 63-68, 70-87, 98-105, 107-111, 116, 117, 119-143 and 157-169 have been rejected under 35 U.S.C. §102(e) as being anticipated by Thompson et al. (U.S. Patent No. 5,824,485, "the '485 patent"). The Examiner remarks that applicant's arguments filed on 9/9/02 are not deemed persuasive and indicates that the main teaching of Thompson et al. is "to generate a diversified enzymatic activity from environmental samples".

Applicant respectfully traverses this rejection. It is respectfully submitted that the claims as presented herein are not anticipated by the '485 patent to Thompson et al. under 35 U.S.C. §102(e).

As was discussed between the Examiner and applicant's attorney during the Examiner Interview, applicant submits that the presently claimed invention is not described or enabled in

the priority documents of the '485 patent to Thompson et al., as is discussed further herein below.

The presently claimed invention is directed to methods for obtaining a modified protein having an improved activity of interest, comprising (a) screening a library of clones to identify the presence of a clone having an activity of interest, wherein each clone of the library contains a nucleic acid obtained without selection from a mixed population of organisms from an environmental sample; (b) subjecting the library to mutagenesis; (c) expressing the library to produce one or more proteins; and (d) screening the proteins to identify a protein having an improved activity of interest compared to the activity identified, thereby obtaining a modified protein having an improved activity of interest.

It is submitted that Thompson et al. fails to teach each and every element of the claimed invention prior to, and at the time of, applicant's presently claimed invention. Because the '485 patent to Thompson et al. fails to disclose each and every element of applicant's claimed invention as of the time of each of its priority application filing dates, this reference fails to anticipate the presently claimed invention.

To anticipate under 35 U.S.C. §102(e), a patent reference must have been filed in the U.S. before the applicant's invention. Accordingly, the effective filing date of the Thompson et al. '485 patent must be earlier than that of the instant application. In addition, under §102, a reference must disclose each and every limitation of a claimed invention. *Apple Computer, Inc. v. Articulate Systems, Inc.*, 234 F.3d 14, 57 USPQ2d 1057 (Fed. Cir. 2000; *Brown v. 3M*, 265 F.3d 1349, 60 USPQ2d 1375 (Fed. Cir. 2001). It is submitted that neither of Thompson et al.'s priority documents discloses or teaches what is presently claimed by the applicant. Thus, Thompson does not anticipate applicant's present claims.

For the Examiner's convenience in assessing the disclosure and teachings of the priority documents of Thompson et al., as well as the disclosure of the '485 patent, the applicant provides herewith (as **Exhibit C**) marked-up copies of the two priority patent applications of Thompson et al., namely, U.S. Serial No. 08/427,348, filed April 24, 1995 ("the '348 application") and U.S. Serial No. 08/427,244, filed April 24, 1995 ("the '244 application"). The teaching and disclosures of these applications and the '485 patent are discussed further below.

As indicated by the highlighted portions of the priority applications, both priority documents reveal a clear lack of disclosure and teaching of methods involving nucleic acids obtained directly from an unselected environmental source. Specifically, the relevant disclosure of selected microorganisms, or selected species of microorganisms, for use in the methods described in the '348 application is found on page 4, lines 5-9; page 7, lines 3-7; page 8, lines 30-35; and page 9, lines 8-12. In addition, the relevant disclosure of selected bacterial species for use in the methods described in the '244 application is found on page 15, lines 13-15; on page 16, lines 19-20; and on page 6, lines 22-24, where marinone is isolated from an estuarine *bacterium*.

It is also apparent that the disclosure in the '485 patent relating to genetic material being obtained from one or more species of donor organisms including those from environmental samples (e.g., Cols. 9, 12 and 13 of the '485 patent) and the "isolation of nucleic acid sequence from soil or other mixed environmental samples (uncultured)", (Section 5.3.6, Col. 41 of the '485 patent) was newly added to the CIP application leading to the '485 patent, i.e., U.S. Serial No. 639,255, at the time of filing the '255 application on April 24, 1996. Indeed, the two priority applications of Thompson et al. are silent with respect to directly obtaining nucleic acid

from donor microorganisms from an environmental sample without an initial isolation or selection process.

The '348 priority application

The '348 priority application of Thompson et al. is concerned with methods of selecting host cells that have been transformed with a construct or vector and which produce a foreign product (or chemical) of interest. The method involves using DNA from one or more selected microorganisms, as clearly disclosed on pages 4 (lines 6-7), 7 (lines 4-7), 8 (lines 29-32) and 9 (lines 10-12) of the specification. The application does not teach or suggest the use of DNA directly obtained without selection from an environmental source, or an uncultured environmental source.

The '244 application

The '244 application involves methods utilizing genetic material obtained from selected microorganisms, for example, select marine microorganisms, to generate new products using the tools of molecular biology, such as particular vector, expression and host systems. (See, page 15, lines 13-15 and page 16, lines 19-20 of the '244 application).

The '244 application is concerned with the generation of metabolic pathways from the genetic material of the selected microorganisms, in which the pathways can function in host cells, which are able to maintain the natural function and architecture of linked functional groups together with their regulatory sequences. (See the '244 application at page 9, lines 20-27). The '244 application discloses providing DNA derived from at least one organism capable of producing at least one chemical substance or activity of interest. (page 4, lines 4-6). To obtain the DNA to prepare libraries, the '244 application teaches that bacterial species, such as marine

species, are selected for the production of a unique compound. (See, the '244 application at page 15, lines 13-15). The '244 application does not teach the presently claimed invention.

U.S. Patent No. 5,824,485 ("the '485 patent")

The '485 patent issued from patent application U.S. Serial No. 639,255 ("the '255 application"), which was filed on April 24, 1996, as a continuation-in-part (CIP) application of both the '348 and the '244 applications. Much new disclosure constituting new matter was clearly added to the '255 CIP application at the time of filing in 1996. Thus, such new disclosure, which did not appear in the priority applications at the time of filing the priority applications, is only given benefit of the filing date of the application in which it was added. Consequently, the new disclosure in the '485 patent is accorded the April 24, 1996 filing date of the '255 CIP application, and not the April 24, 1995 filing date of the two priority applications.

Specifically, disclosure newly added to the '255 application at the time of filing included new detailed description and statements pertaining to the donor organisms used as the source of DNA or nucleic acid in the described methods. While in the two priority applications, the disclosure was limited to selected species of donor organisms or microorganisms, the '255 CIP application newly expanded this disclosure to encompass both selected and unselected donor species.

The new disclosure relating to the unselected nature of donor microorganisms and/or species has been highlighted in the enclosed copy of the '485 patent. More specifically, this disclosure is found in the '485 patent of Thompson et al. at Col. 9, lines 28-30; Col. 9, lines 40-41; Col. 10, lines 46-48; Col. 12, lines 16-19; Col. 12, lines 50-57; Col. 13, lines 57-60; Col. 14, lines 50-52; Col. 29, lines 43-45; Col. 29, lines 60-62; Col. 30, lines 33-37; Col. 41, lines 51-67

to Col. 42, lines 1-54, "5.3.6 Purification of Nucleic Acids from Soil or Other Mixed Environmental Samples"; and Col. 56-Col. 57, "6. Example: Construction and Screening of Combinatorial Gene Expression Library".

The '485 patent includes new disclosure of Thompson et al. that the Examiner considers as supporting a finding of anticipation by the '485 patent. Such disclosure as found in the '485 patent was newly added as of its April 24, 1996 filing date, and therefore does not enjoy the priority date of April 24, 1995. Accordingly, the '485 patent does not anticipate the invention as presently claimed under 35 U.S.C. §102(e).

In view of the foregoing, it is respectfully requested that the rejection under §102(e) over Thompson et al. be withdrawn.

Rejections Under 35 U.S.C. §103

Claims 5-7, 9, 13, 24, 26, 29, 32, 48, 49, 58, 66-71, 85, 86, 89, 106 and 144-156 have been rejected under 35 U.S.C. §103 as being unpatentable over Thompson et al. (U.S. Patent No. 5,824,485, "the '485 patent") in view of the state of the art as exemplified by the cited art, Stemmer et al. (U.S. Patent No. 5,811,238) and Arnold et al. (U.S. Patent No. 5,316,935), as well as all possible material available to one of ordinary skill in the art.

Applicant respectfully traverses the rejection. Because Thompson et al. fails to anticipate under §102(e), it, in turn, cannot make obvious the presently claimed invention, since any relevant teaching in Thompson does not appear until the April 24, 1996 filing date of the application leading to the '485 patent, a date which is after applicant's effective filing date.

None of the cited references alone or in combination make obvious applicant's presently claimed invention considered as a whole.

Stemmer et al. and Arnold et al. fail to compensate for the deficiencies of Thompson et al., and do not teach or suggest applicant's invention as presently claimed. Stemmer discloses reassembly of genes from random DNA fragments resulting in *in vitro* recombination. In accordance with the methods of Stemmer, different combinations of DNA fragments recombine by random crossovers.

Arnold et al. describes the mutation of subtilisin genes to create subtilisins having improved properties, e.g., catalysis. Arnold et al. neither teaches nor describes processes involving nucleic acids that are directly obtained from an unselected environmental source. Based on the teachings of the cited references, there is no motivation for one of skill in the art to combine Thompson with Stemmer and Arnold. Thus, applicant requests that the Examiner reconsider and withdraw this ground of rejection.

New Declaration

Applicant also submits herewith a new Declaration which corrects priority information. The new Declaration is attached hereto as **Exhibit D**.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone at the number provided below.

Applicant: Jay M. Short
U.S. Serial No.: 09/663,620
Filing Date: September 15, 2000

Docket No.: DIV-1140-3

No fees, other than the $465.00 extension of time fee, and the $375.00 fee for filing an RCE, are believed to be due in connection with the filing of this Amendment, IDS and RCE. However, the Commissioner is authorized to debit any necessary fee or credit any overpayment relating to this application to Deposit Account No. 08-0219.

Respectfully submitted,

Date: May 27, 2003

By: _____
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